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| 09/292,217 | 04/15/1999 | STEPHEN D. GILLIES | LEX-004 | 3227 |

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|---|---|
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| ART UNIT | PAPER NUMBER |
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| 1644 | 24 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/292,217 | Applicant(s) GILLIES, STEPHEN D. |
|---|---|---|
| | Examiner Jessica H. Roark | Art Unit 1644 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-9,12-18,20-24,27 and 31-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,12-18,20-24,27 and 31-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 June 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANT'S AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed on 4/2/03 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/2/03 has been entered.

2. Applicant's amendments, filed 4/2/03 (Paper No. 23), is acknowledged.
Claims 3, 10, 11, 19, 25, 26, 28-30, 38 and 39 have been canceled previously.
Claim 37 has been amended.
*Claims* 1, 2, 4-9, 12-18, 20-24, 27 and 31-37 *are pending and being acted upon presently.*

3. This Office Action will be in response to Applicant's arguments, filed 4/2/03 (Paper No. 23). The rejections of record can be found in the previous Office Action (Paper No. 21).

4. The non-statutory double patenting rejection set forth in Paper No. 8 is held in abeyance.

5. Applicant's amendment, filed 4/2/03, has obviated the previous rejection of claim 37 under 35 U.S.C. 112, second paragraph.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

7. Claims 1, 2, 4-9, 12-18, 20-24, 27 and 31-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (Proc. Natl. Acad. Sci. USA 1996; 93:2702-2707, of record) in view of Carron et al. (U.S. Pat. No. 6,171,588, of record).

Applicant's amendments, filed 4/2/03 limits claim 37 in a manner consistent with the claims from which it depends by clarifying that the cytokine is IL-2. The claims as amended still recite a method of inducing a cytocidal immune response against a solid tumor comprising administering an immunoconjugate that binds a target antigen associated with cancer on a target cell in a solid tumor and the cytokine IL-2, and an angiogenesis inhibitor that is an agent having binding affinity for $\alpha_v\beta_3$ integrin, and the corresponding composition.

Applicant's arguments, filed 4/2/03, have been fully considered, but have not been found convincing.

Applicant's arguments are addressed following a reiteration of the rejection of record.

As previously noted, Becker et al. teach immunoconjugates comprising an antibody binding site specific for a target antigen associated with cancer and expressed on a target cell in solid tumor (i.e., either the EGF receptor or ganglioside $GD_2$ expressed by melanoma cells) and the cytokine IL-2 (see entire document, e.g., "Cell lines and Reagents" in Materials and Methods). Becker et al. teach the use of these immunoconjugates in inducing a cytocidal immune response against the solid tumor (see entire document).

Becker et al. teach that the immunoconjugate have the IL-2 cytokine attached to the carboxyl end of the antibody $C\gamma1$ gene (see e.g. "Cell lines and Reagents" in Materials and Methods). Thus the immunoconjugates of Becker et al. comprise in an amino-terminal to carboxy-terminal direction the antibody binding site comprising the immunoglobulin variable region capable of binding the target antigen, the immunoglobulin CH1 domain, an immunoglobulin CH2 domain, and immunoglobulin CH3 domain, and IL-2.

Becker et al. teach that IL-2 is one of the most potent antitumor cytokines known (e.g. page 2702, first column), and that immunoconjugates which combine a tumor specific antibody and IL-2 are more effective than administration of the antibody and IL-2 as separate compounds (e.g., page 2705, bridging paragraph and following paragraph).

Becker et al. do not teach compositions combining the immunoconjugate with an angiogenesis inhibitory having binding affinity for $\alpha_v\beta_3$ integrin, nor methods of using the combination of compositions.

As also previously noted, Carron et al. teach compositions having binding affinity for $\alpha_v\beta_3$ integrin (see entire document). Carron et al. teach that compositions having binding affinity for $\alpha_v\beta_3$ integrin are useful in methods of inhibiting solid tumor growth (see entire document, but especially columns 3-5 and 19-20).

Carron et al. also teach that compositions having binding affinity for $\alpha_v\beta_3$ integrin may be combined with other pharmaceutical compositions or added to established anti-cancer chemotherapeutic or biotherapeutic regimens, including therapies involving the administration of IL-2 in the biological therapy of cancer (see especially column 13).

The Examiner maintains that the ordinary artisan at the time the invention was made would have therefore found it obvious to combine the composition taught by Becker et al. with the composition taught by Carron et al. Further, the ordinary artisan would have found it obvious to use the composition resulting from the combination of the immunoconjugate of Becker et al. and the compositions having binding affinity for $\alpha_v\beta_3$ integrin of Carron et al. for use in an improved method of inducing a cytocidal immune response against a solid tumor. The timing of the administration of each component (either co-administration or sequential administration) would also have been obvious to the ordinary artisan at the time the invention was made and a matter of routine optimization.

Given the teachings of Carron et al. that the compositions having binding affinity for $\alpha_v\beta_3$ integrin should be combined with IL-2 based therapies of cancer, the ordinary artisan would clearly have been motivated to select the established IL-2 based therapy as taught by Becker et al. for combining with that of Carron et al. Further, given that both the immunoconjugate of Becker et al. and the compositions having binding affinity for $\alpha_v\beta_3$ integrin of Carron et al. are taught individually to be useful for the same purpose (therapy of cancer cells, including solid tumors) the ordinary artisan would have had a reasonable expectation the combination would induce a greater cytocidal immune response against the cancer cell, including cancer cells in a solid tumor, that was greater than a response induced by the immunoconjugate alone.

Applicant argues that there is no motivation to combine the references because, although Applicant acknowledges that Carron et al. teach combining the $\alpha_v\beta_3$ integrin binding composition with other therapeutic regimens, Carron et al. fail to mention or suggest combining with an immunoconjugate and Becker et al. do not teach combination therapy.

However, Carron et al. do teach combining the $\alpha_v\beta_3$ integrin binding composition with other established anti-cancer chemotherapeutic or biotherapeutic regimens. In view of the teaching of Becker et al., the ordinary artisan would conclude that the IL-2 immunoconjugate was such an anti-cancer biotherapeutic. Applicant is again reminded that the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 217 USPQ 1, 5 - 6 (Fed. Cir. 1983).

Applicant also comments that the combination represents only an "obvious to try" scenario for which the references fail to provide a reasonable expectation of success. However, the teachings provide the individual compositions, show that each individually works in a method of inhibiting tumor growth and provide direction to combine individual anti-cancer therapeutics. Since both compositions work individually in the instantly claimed method, the ordinary artisan would have had a reasonable expectation that the compositions would also work in the instant methods when combined.

Applicant again argues in the Remarks filed 4/2/03 that the instantly recited combination shows unexpected properties with respect to an effect on tumor cell growth, as evidenced by Lode et al. (Proc. Natl. Acad. Sci. USA 1999; 96:1591-1596, of record). Applicant points to a "synergistic efficacy" observed by Lode et al. as evidence that these results are unexpected.

While the Examiner acknowledges that in certain assays of Lode et al. (e.g., reduction of metastases in Figures 4 and 5) the effect of combination therapy may be synergistic rather than simply additive; it is also noted that the instant claims recite induction of a cytocidal immune response against a solid tumor/cancer. The data most relevant to the instantly claimed method appears to be that of Figure 1 of Lode et al, which show an effect that appears to be additive. In addition, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. In the instant case, these results do not appear to be unexpected in view of the teachings of the references.

In addition, even were the results unexpected, evidence of unexpected results are not necessarily sufficient to overcome a prima facie case of obviousness. Although the record may establish evidence of secondary considerations which are indicia of nonobviousness, the record may also establish such a strong case of obviousness that the objective evidence of nonobviousness is not sufficient to outweigh the evidence of obviousness. Newell Cos. v. Kenney Mfg. Co., 864 F.2d 757, 769, 9 USPQ2d 1417, 1427 (Fed. Cir. 1988), cert. denied, 493 U.S. 814 (1989); Richardson-Vicks, Inc., v. The Upjohn Co., 122 F.3d 1476, 1484, 44 USPQ2d 1181, 1187 (Fed. Cir. 1997) (showing of unexpected results and commercial success of claimed ibuprofen and psuedoephedrine combination in single tablet form, while supported by substantial evidence, held not to overcome strong prima facie case of obviousness).

In the instant case, even were the results unexpected, the combination of references appears to provide a sufficiently strong prima facie case that unexpected results still would not be sufficient to overcome the rejection of record. The rejection is therefore maintained.

8. No claim allowed

9. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
June 12, 2003

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